REMARKS/ARGUMENTS

Claims 1-48 are pending in the application.

Claims 1-48 stand rejected under 35 USC §103(a) as unpatentable over Lehto et al., WO 99/54730 ("Lehto") in view of Verwaerde et al., US Published Application No. 2004/0038227 ("Verwaerde"). The examiner contends that Lehto teaches a method of performing biochemical analysis using small amounts of liquid sample that comprises the merging of two sample solutions comprising a drug candidate and a drug target on a substrate using electrostatic forces, including the use of parallel electrodes arranged on a substrate for facilitating the transport and manipulation of sample droplets during processing and analysis, and the use of temperature controlled environment. The examiner acknowledges the failure of Lehto to teach detecting and comparing the heats of reaction during the analysis, but looks to Verwaerde for the teaching of the benefits to use of a microcalorimeter. Applicants traverse.

The independent claims of the subject application, claims 1 and 26, require that a target compound including at least one binding site of interest and at least one binding site to be avoided be merged, or contacted, with a test ligand at two positions on an enthalpy measuring device, and that a blocking agent also be used at only one of the two positions. The purpose of this method is to selectively identify substrates for enzymes that may be used in the discovery of drugs candidates. This differs from known ligand-enzyme binding site detection methods, in that ligands, which may bind to multiple sites, may bind to the wrong, or unwanted, sites. The claimed invention employs blocking agents to inhibit binding to unwanted sites. The desired binding site is often very important with regard to drug discovery, as is discussed in the background of the specification. This invention, as claimed, detects desired binding affinities at specific substrate sites as opposed to blocked non-substrate sites based on calorimetry. In other words, calorimetry is used to discover substrates in the presence of blocking compounds for the ligands as they react with the target compounds being

tested. Measuring enthalpy in the presence of the blocking compound and in the absence of the blocking compound provides the needed identification of sites and therefore substrates.

Lehto does not teach or even suggest the discovery of substrates in the presence of blocking compounds for the ligands as they react with the target compounds being tested, nor the use of calorimetry to do the same. Lehto make no attempt at measuring enthalpy, let alone doing so in the presence of a blocking compound and in the absence of the blocking compound to determine or discover interaction information useful in the discovery of new pharmaceutical agents.

The examiner cites Verwaerde for a teaching to the use of calorimetry to detect changes in enthalpy. While this is accurate, the reference teaches nothing more than that in the context of the subject application. It is unlikely that one skilled in the art, aware of the method of Lehto, would look to Verwaerde given that Lehto is detecting fluorescence, and therefore has no interest in detecting changes in enthalpy caused by a reaction of interest. However, if one did look to combine the teachings of these references, one would achieve a method to transport sample solutions through a series of positions on a device using an electrostatic field to affect such transport, and then detect a change in enthalpy during a reaction of the sample solutions. Absent from the combination of these teachings is any suggestion to compare the reaction of a ligand solution and a target solution first in the presence of a blocking agent and then in the absence of the blocking agent in order to discover viable substrates for pharmaceutical purposes, or how to detect the same using calorimetry. The combination does not teach or suggest these limitations as set forth in the independent claims of the subject application. In addition, each dependent claim is considered to include all limitations of the independent claim from which it ultimately depends, as well as any intervening claim limitations. Therefore, given that the references do not teach the noted limitations of independent claims 1 and 26, specifically the use of a blocking agent to create a change in enthalpy detectable by a nanocalorimeter, this feature being used to discover suitable

substrates for use in discovering, for example drug candidates, the references are equally inapplicable to the dependent claims of the subject application.

Based on the foregoing, it is respectfully requested that the rejection of claims 1-48 over the combination of Lehto in view of Verwaerde be reconsidered and withdrawn. Should the examiner wish to discuss the foregoing amendment and/or arguments, a telephone call to the undersigned attorney would be welcome.

Respectfully submitted,

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